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GRANULOCYTIC RECOVERY IN THE POLYCYTHEMIC DOG TREATED WITH ENDOTOXIN POSTIRRADIATION

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ARMED FORCES RADIOBIOLOGY RESEARCH INSTITUTE
Defense Nuclear Agency
Bethesda, Maryland

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A. G. PRATT
R. J. EMERSON
S. J. BAUM

S. J. BAUM
Chairman
Experimental Pathology Department

M. I. VARON
Captain MC USN
Director

ARMED FORCES RADIOBIOLOGY RESEARCH INSTITUTE
Defense Nuclear Agency
Bethesda, Maryland

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FOREWORD
(Nontechnical summary)

Injury to the blood-forming tissues is responsible for the sickness following radiation doses of sufficient magnitude to kill most of the animals exposed. There are very few treatments which will accelerate recovery of the ability to produce blood cells, particularly those responsible for combating infection (granulocytes) and bleeding (platelets). Of the three major blood cell types, red cells (erythrocytes) have the longest life in the blood and there appears to be an emphasis toward producing these cells after radiation rather than the shorter lived granulocytes and platelets.

This study was designed to measure effects on postirradiation granulocyte and platelet recovery when a combined approach aimed at suppressing erythrocyte production before irradiation and stimulating granulocyte production by the administration of typhoid vaccine (endotoxin) following radiation exposure was employed. Red cell production was suppressed by transfusion of blood from donor dogs on three occasions during the week prior to irradiation and endotoxin was given 24 hours after irradiation. This treatment combination was compared to a control group receiving no treatment and to the effect obtained with each treatment used alone.

During the middle of the 2nd week following radiation exposure, the group receiving both transfusions and endotoxin had significantly higher numbers of granulocytes in their blood compared to the other three treatment groups. No treatment combination appeared to affect the two periods of low counts at the beginning and end of the 2nd week. Recovery during the 3rd and 4th weeks was accelerated by endotoxin and retarded by transfusion, with the net effect being no difference between the group receiving both treatments and the group which was untreated.

Platelet concentration in the blood was reduced in all groups during the 2nd and 3rd weeks following radiation exposure. Endotoxin did not appear to modify this pattern while transfusion seemed to produce a more marked drop in platelet numbers. This decrease in platelets appeared to be associated with an increase in the size of the spleen, an organ which has been described previously as a reservoir for the platelet, particularly when enlarged.

ABSTRACT

This experiment was designed to test the hypothesis that, in hypertransfused dogs with suppressed erythropoiesis, endotoxin-induced increased myelopoietic stimulation 24 hours after irradiation would enhance leukocytic recovery. The treatment combination of transfusion polycythemia and endotoxin was compared to a control group receiving no therapy or to the results obtained from groups of dogs receiving each treatment alone. The radiation exposure was 150 rads of total body x rays. An accentuated abortive rise in the group receiving the combined treatment, accelerated recovery in both groups receiving endotoxin, and impaired leukocytic recovery in the polycythemic animals were observed. Accentuated depression of platelets and splenic enlargement inversely correlated with the platelet levels were observed in the animals receiving transfusion therapy regardless of whether they received endotoxin. It is felt that the data support the concept of interdependence between the various cell lines of hematopoiesis in an experimental model not previously described.

I. INTRODUCTION

Death following exposure to doses of ionizing radiation below 1000 rads is usually caused by failure of hematopoiesis, leading to infection and hemorrhage from lack of the short-lived granulocytes and platelets.[7] The concept of a common stem cell repopulating the erythrocytic, megakaryocytic and myelocytic cell lines after irradiation has received considerable support.[19,21] Despite the greater need for granulocytes, Hellman et al.[15] have demonstrated that by the 4th day after irradiation, there is a marked emphasis on repair of erythropoiesis. Transfusion polycythemia prior to irradiation for erythropoietic suppression does not appear sufficient, by itself, to increase production of granulocytes in the dog.[4] Although it was possible to achieve a marked accentuation of the granulocyte abortive rise by administration of endotoxin before irradiation,[1] Ainsworth and Mitchell were not able to produce a similar increase when typhoid vaccine was given to the dog 24 hours after irradiation, despite an increase in survival.[2]

The present study was conceived to test the hypothesis that a combination of erythropoietic suppression by preirradiation induction of transfusion polycythemia and granulopoietic stimulation with endotoxin administered after irradiation might result in enhancement of postirradiation granulocyte recovery.

II. METHODS

Healthy, purebred, AKC registrable beagles, 12 - 18 months of age were utilized in this study. The dogs were bred and boarded at ANTEC Corporation (Leesburg, Virginia) where immunization for rabies and distemper was performed. At least 2 weeks before transfusion, the dogs were transferred to temperature-controlled animal rooms

at the Armed Forces Radiobiology Research Institute. The animals were then examined for parasite infestation, and necessary veterinary care was provided. They were maintained individually in stainless steel cages, fed kibbled laboratory dog food supplemented once a week with a high protein canned meat ration, and provided with fresh water ad libitum.

Thirty-one dogs were randomly assigned to the following four treatment groups: control (C), preirradiation hypertransfusion only (P), endotoxin after irradiation only (E), and a combination of both (P + E). Group (P) contained seven animals, the remaining groups consisted of eight animals each.

All dogs were irradiated with a radial beam generator as the x-ray source. It has the following physical factors: 250 kVp, 30 mA, 1.2 mm Be + 0.95 mm Cu filtration (HVL - 1.9 mm Cu); and target to subject midline distance 105 cm. The absorbed dose rate at the center of the dogs was 20 rads/minute. Bilateral exposure conditions were achieved as described previously.[5]

The endotoxin employed was typhoid and paratyphoid A and B (Parke-Davis) containing 1.5×10^9 killed organisms per milliliter and was given 24 hours postirradiation.

Polycythemia was achieved in the designated recipients by three transfusions, each containing about 250 ml of packed erythrocytes from beagle donors, on the 7th, 5th and 2nd days before irradiation.

Before transfusion, and daily after irradiation, hematologic parameters were obtained by standard techniques including microhematocrit, red and white cell counts using the Coulter counter (Coulter Electronics, Hialeah, Florida), differential counts of peripheral blood smear, and platelet counts using the phase contrast technique of

Brecher and Cronkite[9] and the technique described by Nakeff and Ingram[18] involving density separation with silicone fluid and counting with the Coulter counter.

Four dogs from each of the four groups described above were sacrificed by electrocution on the 50th day following radiation exposure and the weights of the spleens were determined. The commonly employed use of a barbiturate for sacrifice was avoided because it causes acute splenic congestion.

The characteristic points of the postirradiation granulocyte course, i.e., the two minima and the abortive peak between (vide infra), were estimated in each animal using several observations in each region to obtain a smooth curve (by regression analysis) utilizing the least squares method to fit polynomials up to degree three. Statistical techniques included the Mann-Whitney, Kolmogorov-Smirnov, and Kendall rank correlation methods.[20] Probability results are given for use of the sign test unless otherwise stated.[20]

III. RESULTS

Hematocrits averaged about 65 percent at the time of irradiation and remained elevated for 2 weeks. Previous work in this laboratory has demonstrated a 70 percent decrease in ^{59}Fe incorporation in dogs, with the transfusion technique described above.[6]

The two groups treated with endotoxin demonstrate mobilization of granulocytes on days 2 and 3 (Figure 1). All groups experience a nadir between days 7 and 9, with the average of the least squares fitted minima for all animals being day 8. An abortive rise follows with maximum response seen between days 10 and 12. A second period of low granulocyte levels occurs in the 3rd week, with the average time to

minimum for all animals being 17 days. Final recovery then follows in the 4th and 5th weeks.

Comparison of the group averages during the abortive rise over the period from the average first minimum on day 8 to the second minimum on day 17, demonstrates a significantly increased concentration of circulating granulocytes in the combined treatment group on all days compared to the endotoxin treated group ($p < 0.003$) and on all but the 9th day compared to the two groups not receiving endotoxin ($p < 0.03$). The single point estimates of the peak abortive rise obtained for each animal by curve fitting also demonstrate the superiority of combined treatment compared to the three other groups, using the Kolmogorov-Smirnov test ($p < 0.02$).

During the final recovery period following day 17, the combined treatment group average granulocyte counts are higher than those of the group treated with transfusion alone on 14 out of 14 days ($p < 0.001$), essentially the same as those of the untreated control group, and significantly lower than those of the group treated with endotoxin alone (12 out of 14 days, $p < 0.05$).

Figure 2 presents the average of the two groups receiving endotoxin in comparison to the two not receiving this treatment; the treated groups are noted to have higher counts than the untreated groups on 9 out of 10 days ($p < 0.05$) during the abortive rise and above the untreated groups on 14 out of 14 days ($p < 0.001$) during final recovery.

The average of the two groups whose treatment included transfusion polycythemia is illustrated in Figure 3 in comparison to the average of untreated groups. No difference between the groups is apparent during the abortive rise, while there appears to be retardation of recovery (12 out of 14 days, $p < 0.05$) in the transfused animals.

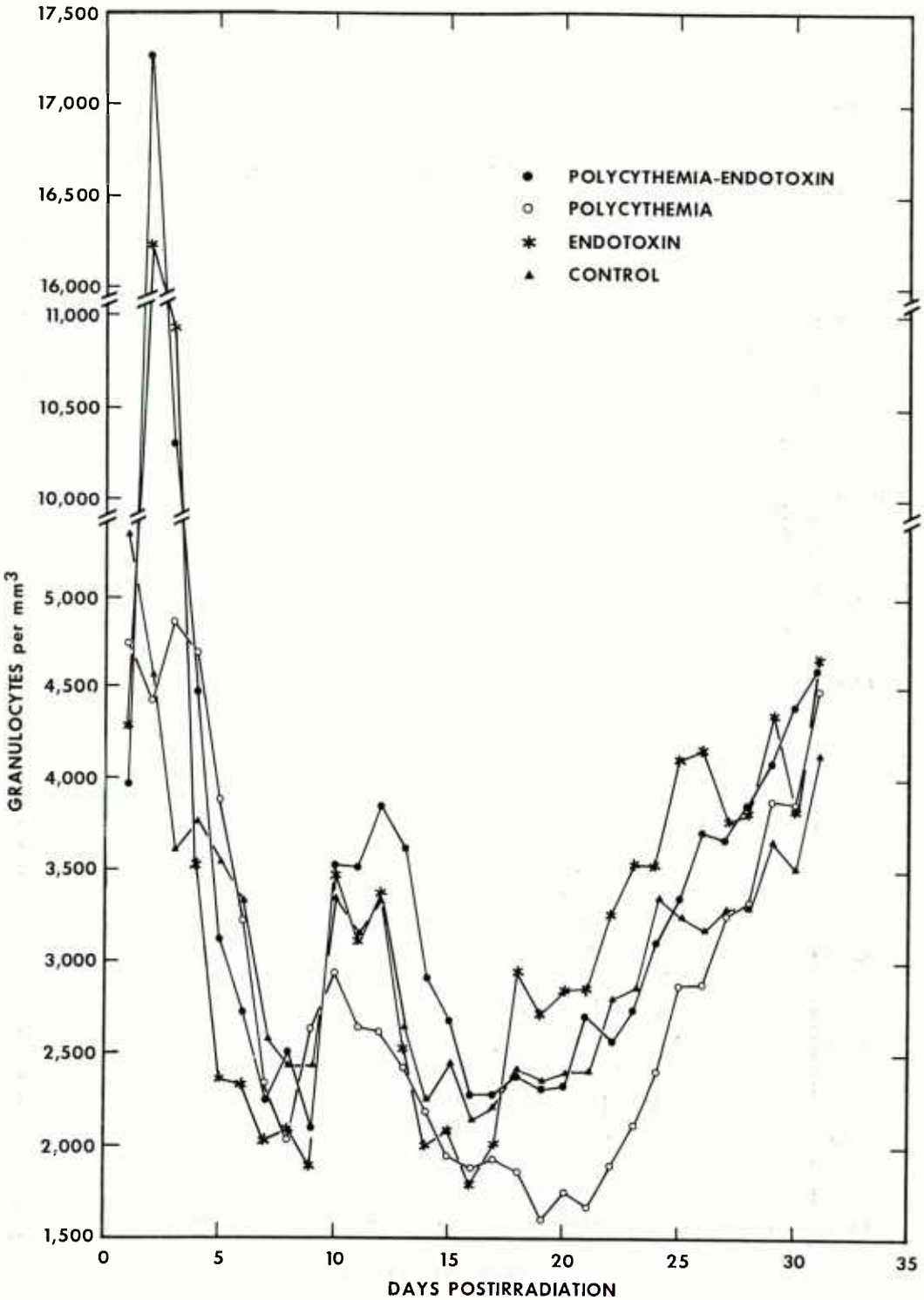

Figure 1. Postirradiation granulocyte values in dogs exposed to 150 rads of x rays

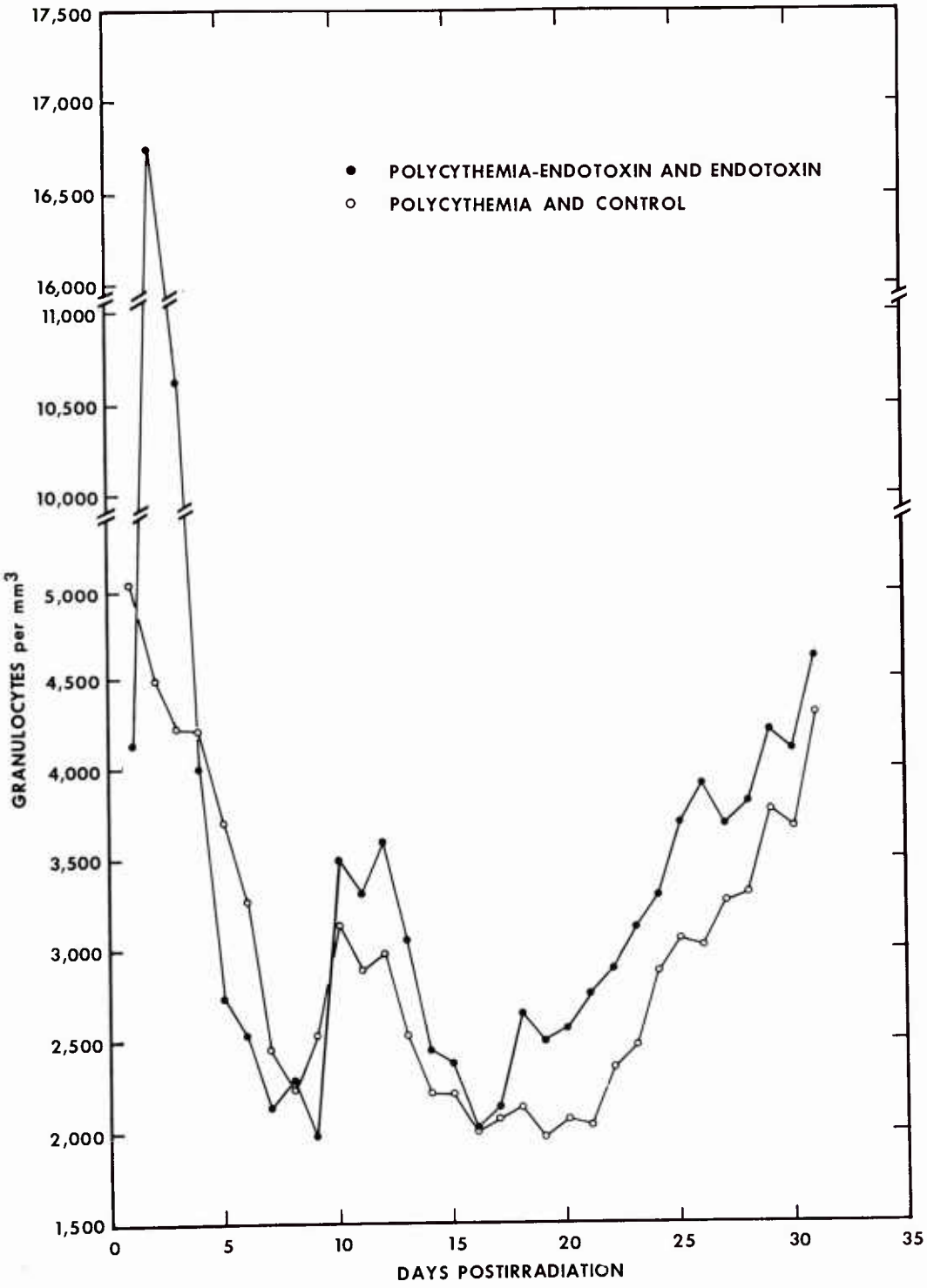

Figure 2. Effect of endotoxin therapy postirradiation on granulocytes in dogs

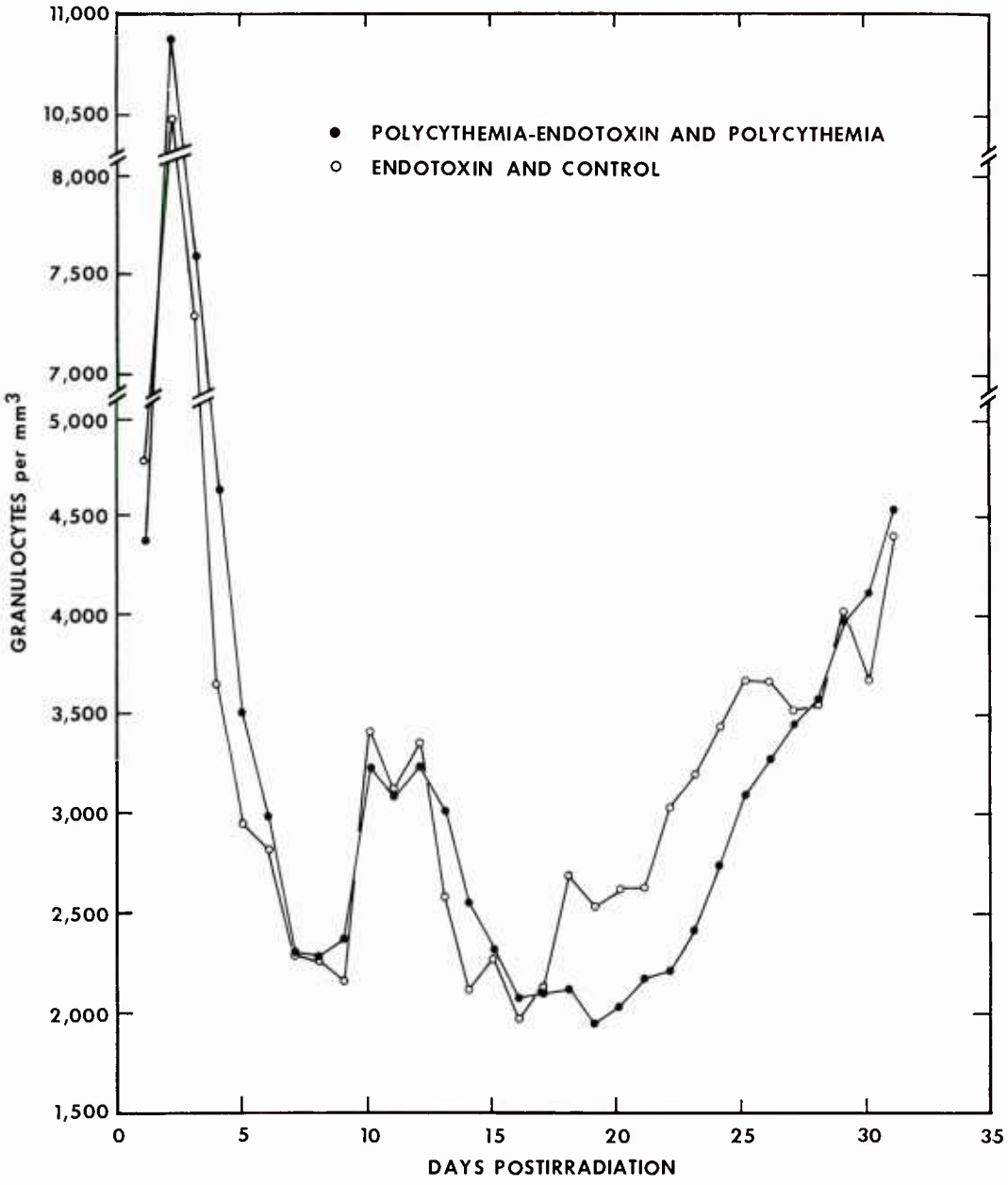

Figure 3. Postirradiation granulocyte values in polycythemic animals

As shown in Figure 4, the average of the combined treatment group and the untreated controls is higher during the abortive rise than the average of the two groups receiving one treatment only (9 out of 10 days, $p < 0.05$) which suggests an interaction

or synergism of the two treatments and requires cautious interpretation of the conclusions regarding the difference noted between endotoxin treated and untreated groups during the abortive rise (Figure 2). No such interaction is seen in the period of final recovery.

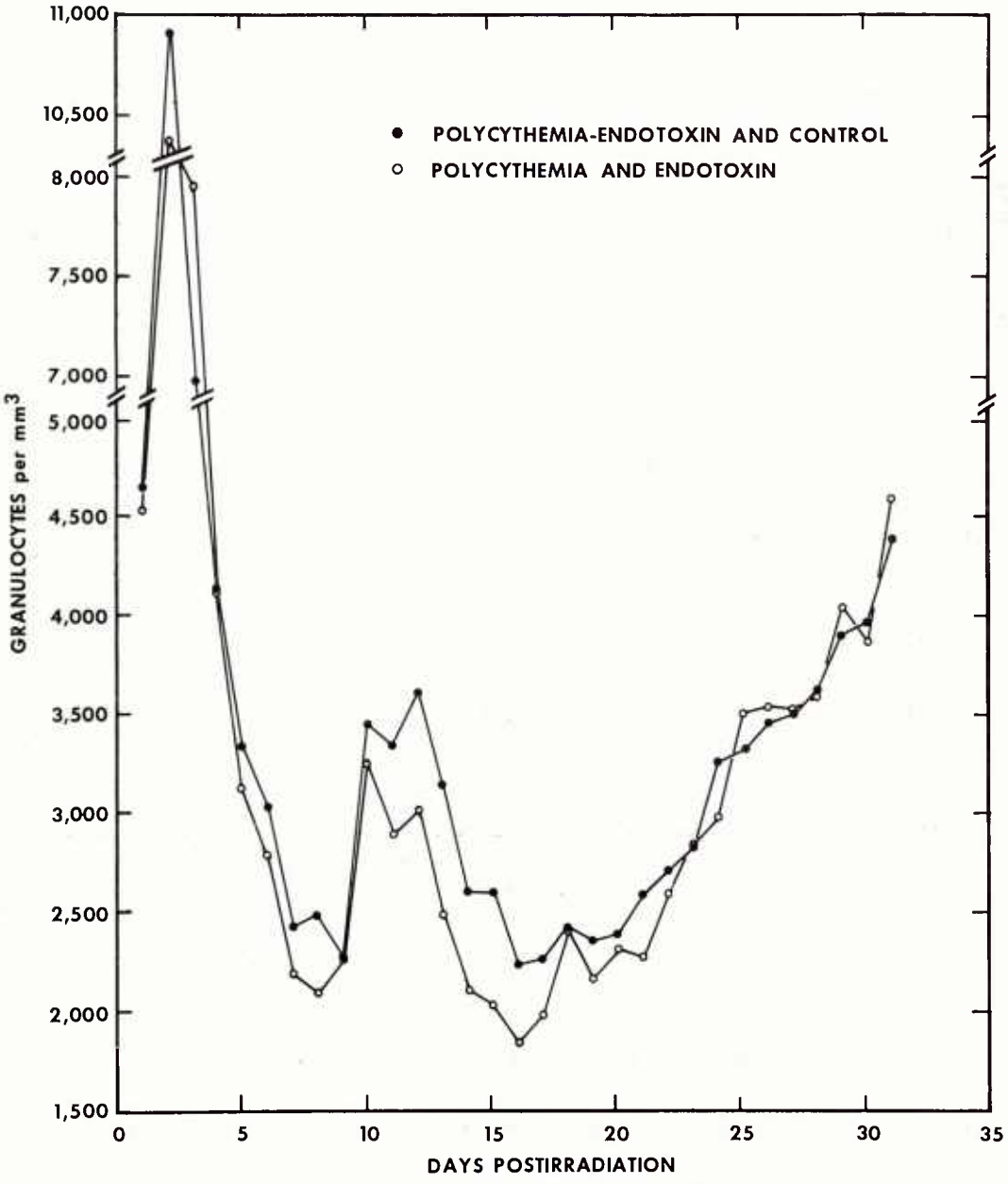

Figure 4. Interaction of polycythemia and endotoxin therapy on postirradiation granulocyte values in dogs

Figure 5 illustrates the postirradiation course of the platelet counts, with all groups showing no significant change before day 5. Exponential disappearance of platelets then proceeds until day 12 when a relatively level plateau is seen extending to day 21, after which recovery is seen. During the 10-day plateau of minimum counts, each animal's daily platelet counts were averaged and a significantly ($p<0.05$ by Mann-Whitney) lower level of the plateau was identified in the hypertransfused groups despite the fact that the animals were no longer polycythemic after the 2nd week.

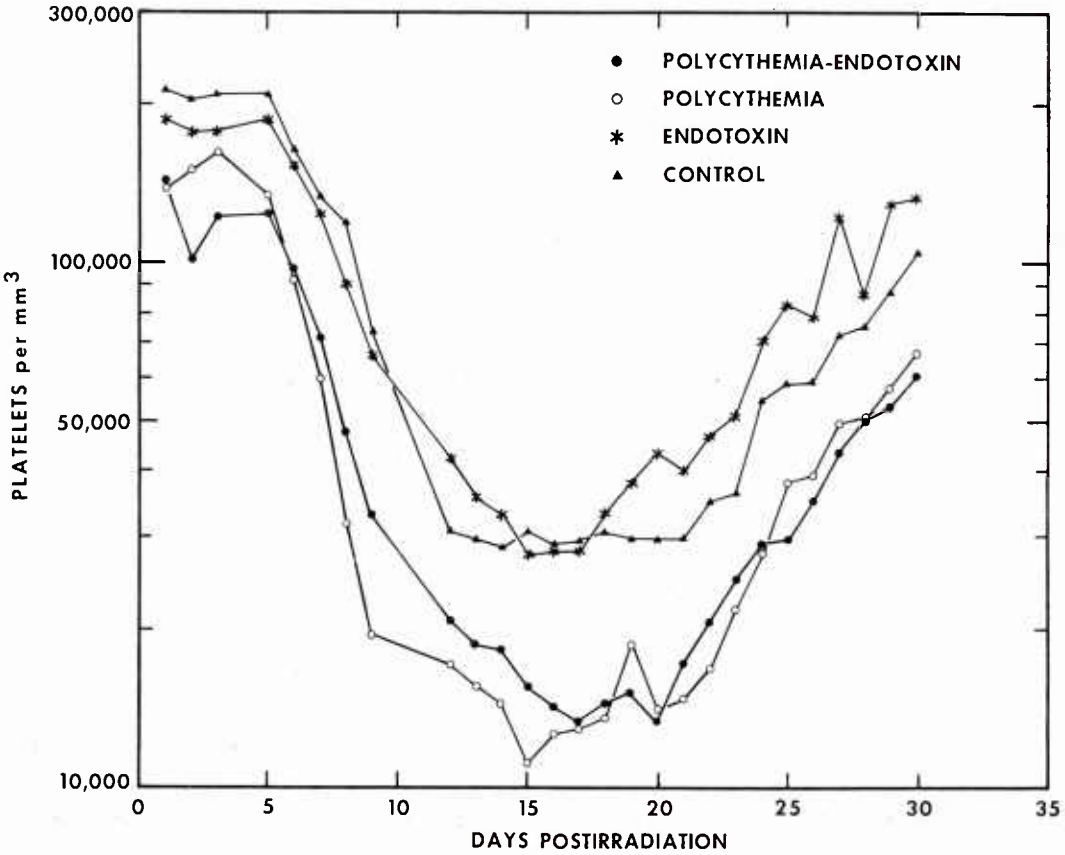

Figure 5. Postirradiation platelet values in dogs exposed to 150 rads of x rays

The spleen weights of the animals from the last two replicates of all groups (4 dogs each) were determined after electrocution on the 50th postirradiation day and

demonstrated a significantly greater ratio of spleen to body weight in both transfused groups ($p < 0.05$ by Mann-Whitney). An inverse correlation of spleen weight with platelet count during the plateau from days 12 - 21 ($p < 0.05$) and with counts on day 40 ($p < 0.02$) was also noted, using the Kendall rank correlation method. No correlation of spleen size with granulocyte levels could be demonstrated.

IV. DISCUSSION

These studies, addressed to the possibility of accelerating postirradiation granulocyte recovery, suggest that suppression of erythropoiesis alone prior to irradiation has no significant effect on the granulocyte abortive rise and actually is associated with reduced levels of granulocytes during final recovery.

Conversely, endotoxin administered 24 hours postirradiation appears to increase granulocyte levels during final recovery. However, in view of the interaction of the two treatments during the abortive recovery, endotoxin may not be said to have a significant effect alone during this period; treatment with endotoxin must occur in the presence of erythropoietic suppression for the occurrence of significant enhancement in the granulocyte abortive recovery. This synergism of the two treatments suggests that erythropoietic suppression makes available multipotential stem cells for myelopoiesis. However, this increase in granulocyte production will only occur when a demand or signal for increased production is initiated, as is presumably the case with the massive mobilization of granulocytes from the bone marrow caused by endotoxin.[22]

Evidence to support the concept of a common stem cell has been presented by Wu et al.[21] and Nowell et al.[19] Diminished granulopoietic recovery following irradiation of anemic animals has been demonstrated by Hellman and Grate,[14] Bradley et al.[8] and

Harris et al.[13] Morley et al.[17] have recently reported that in two groups of irradiated mice, who had one hind leg shielded, the group which was made polycythemic (by hypoxia) prior to irradiation demonstrated enhanced recovery of early granulopoietic cells in the marrow of the shielded leg and increased numbers of peripheral granulocytes. There appears to be a contrast with our findings where polycythemic suppression of erythropoiesis was not sufficient alone to enhance granulocytic recovery. Two obvious differences between the experimental designs should be emphasized: the use of different species and the technique employed for erythropoietic suppression. Morley et al.[17] subjected mice to hypoxia and irradiated them 6 days after return to ambient conditions. At this time, the animals were noted to have peripheral granulocyte and marrow myelopoietic precursor levels about twice those seen in the nonpolycythemic animals.

It is also about this time that polycythemic mice recovering from hypoxia demonstrate the maximum production of colony forming units (CFU) to about 200 percent of control values.[16] Presumably, then, hypoxia-induced polycythemia confers a certain advantage on the mice at the time of radiation exposure which would not apply to dogs whose erythropoiesis is suppressed with transfusion alone since hypertransfused mice have normal numbers of transplantable CFU.[10]

In the present study, a significantly greater reduction in numbers of platelets following irradiation occurred in the two transfused groups. In view of the distinctly larger spleens in the transfused animals and the inverse correlation of spleen size with the platelet concentration, it is suggested that splenic enlargement accounts for the reduction in platelet levels. In support of this, the reports of Aster[3] and de Gabriele

and Penington[11] have demonstrated a strong inverse relationship between circulating numbers of platelets and splenic hypertrophy induced experimentally in the rat with intraperitoneal injections of methylcellulose. They have shown, as has Harker,[12] that sequestration of an exchangeable pool of platelets in the hypertrophied spleen may account for as much as 60 percent of total platelets.

It appears, then, that enhanced final recovery of peripheral granulocyte levels with postirradiation endotoxin therapy in the dog is possible, as Ainsworth and Mitchell[2] demonstrated at higher doses of radiation. Neither their work nor ours demonstrates augmentation of the abortive rise during the 2nd week, with endotoxin alone, as is seen with treatment prior to irradiation. On the other hand, in the present study, polycythemic animals with suppressed erythropoiesis were able to respond to endotoxin administration, following irradiation, with a significant increase in the concentration of circulating granulocytes during the 2nd week. No further beneficial effect from the combined treatment was observed beyond the 2nd week.

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Priv.-Doz. Dr. O. Messerschmidt, Radiologisches Institut der Universität, 78 Freiburg im Breisgau, Albertstrasse 23, Germany (1)
Dr. Helmut Mitschrich, Akademie des Sanitäts- und Gesundheitswesens der Bundeswehr, Spezialstab ATV, 8 München, Schwere Reiterstrasse 4, Germany (2)
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Puerto Rico Nuclear Center, ATTN: Reading Room, College Station, Mayaguez, Puerto Rico 00708 (2)
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This experiment was designed to test the hypothesis that, in hypertransfused dogs with suppressed erythropoiesis, endotoxin-induced increased myelopoietic stimulation 24 hours after irradiation would enhance leukocytic recovery. The treatment combination of transfusion polycythemia and endotoxin was compared to a control group receiving no therapy or to the results obtained from groups of dogs receiving each treatment alone. The radiation exposure was 150 rads of total body x rays. An accentuated abortive rise in the group receiving the combined treatment, accelerated recovery in both groups receiving endotoxin, and impaired leukocytic recovery in the polycythemic animals were observed. Accentuated depression of platelets and splenic enlargement inversely correlated with the platelet levels were observed in the animals receiving transfusion therapy regardless of whether they received endotoxin. It is felt that the data support the concept of interdependence between the various cell lines of hematopoiesis in an experimental model not previously described.

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